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THOMAS, MIA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/817,213	ARINI ET AL.	
	Examiner	Art Unit	
	Mia M. Thomas	2609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☒ Claim(s) *3,10,11,17,18 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The USPTO "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility" (Official Gazette notice of 22 November 2005), Annex IV, reads as follows:

> Claims that recite nothing but the physical characteristics of a form of energy, such as a frequency, voltage, or the strength of a magnetic field, define energy or magnetism, per se, and as such are nonstatutory natural phenomena. O'Reilly, 56 U.S. (15 How.) at 112-14. Moreover, it does not appear that a claim reciting a signal encoded with functional descriptive material falls within any of the categories of patentable subject matter set forth in Sec. 101.
>
> ... a signal does not fall within one of the four statutory classes of Sec. 101.
>
> ... signal claims are ineligible for patent protection because they do not fall within any of the four statutory classes of Sec. 101.

Claim 35 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter as follows. Claim 35 defines a "data carrier storing the computer software of claim 34", with descriptive material. While "functional descriptive material" may be claimed as a statutory product (i.e., a "manufacture") when embodied on a tangible computer readable medium, a data carrier embodying that same functional descriptive material is neither a process nor a product (i.e., a tangible "thing") and therefore does not fall within one of the four statutory classes of § 101. Rather, "signal" is a form of energy, in the absence of any physical structure or tangible material.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The USPTO "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility" (Official Gazette notice of 22 November 2005), Annex IV, reads as follows:

> Descriptive material can be characterized as either "functional descriptive material" or "nonfunctional descriptive material." In this context, "functional descriptive material" consists of data structures and computer programs, which impart functionality when employed as a computer component. (The definition of "data structure" is "a physical or logical relationship among data elements, designed to support specific data manipulation functions." The New IEEE Standard Dictionary of Electrical and Electronics Terms 308 (5th ed. 1993).) "Nonfunctional descriptive material" includes but is not limited to music, literary works and a compilation or mere arrangement of data.
>
> When functional descriptive material is recorded on some computer-readable medium it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized. Compare In re Lowry, 32 F.3d 1579, 1583-84, 32 USPQ2d 1031, 1035 (Fed. Cir. 1994) (claim to data structure stored on a computer readable medium that increases computer efficiency held statutory) and Warmerdam, 33 F.3d at 1360-61, 31 USPQ2d at 1759 (claim to computer having a specific data structure stored in memory held statutory product-by-process claim) with Warmerdam, 33 F.3d at 1361, 31 USPQ2d at 1760 (claim to a data structure per se held nonstatutory).
>
> In contrast, a claimed computer-readable medium encoded with a computer program is a computer element which defines structural and functional interrelationships between the computer program and the rest of the computer which permit the computer program's functionality to be realized, and is thus statutory. See Lowry, 32 F.3d at 1583-84, 32 USPQ2d at 1035.

Claim 34 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter as follows. Claim 34 defines "computer software arranged to perform the method of claim 1", embodying functional descriptive material. However, the claim does not define a computer-readable medium or memory and is thus non-statutory for that reason (i.e., "When functional descriptive material is recorded on some computer-readable medium it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized" – Guidelines Annex IV). That is, the scope of the presently claimed computer software can range from paper on

which the program is written, to a program simply contemplated and memorized by a person. The examiner suggests amending the claim to embody the program on "computer-readable medium" or equivalent in order to make the claim statutory. Any amendment to the claim should be commensurate with its corresponding disclosure.

Claim Objections

Claim Objections - 37 CFR 1.75(a)

3. The following is a quotation of 37 CFR 1.75(a):

> The specification must conclude with a claim particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention or discovery.

4. Claims 3,10, 11,17,19 are objected to under 37 CFR 1.75(a) as failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention or discovery.

Regarding Claim 3, the term "said second set of cells" at page 50, line 24 lacks an antecedent basis. However, it appears from the context of the claim when read in light of the specification that "said second set of cells" is in fact referring to the "...classifying a second set of cells into subpopulations" first introduced at page 50, line 17 of claim 1; and this will be assumed for examination purposes:

Claim 3: The method of claim 1, wherein classifying *said second set of cells* comprises comparing the measurements for cells in the second set with the cell cycle phase classifying data derived from classification of the first set of cells.

Regarding Claim 17, the term "said step of receiving image data" at page 52, line 11 lacks an antecedent basis. However, it appears from the context of the claim when read in light of the specification that "said step of receiving image data" is in fact referring to the "...method of claim 1, ...wherein said step of receiving said image data

comprises ..." first introduced at page 51, line 32 of claim 14; and this will be assumed for examination purposes:

Claim 17: The method of claim 1, wherein classifying *said second set of cells* comprises comparing the measurements for cells in the second set with the cell cycle phase classifying data derived from classification of the first set of cells.

Regarding Claims 10 and 11, the term "predominately" is considered narrow language and is a relative term, which renders the claim(s) indefinite in accordance with the interpretation of the claimed subject matter. The term "predominately" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. How close is "predominately close?" Where would one of ordinary skill in the art measure a predominately cyotplasimic or nuclear area of a cell? Without a firm grasp of what constitutes "predominately", one cannot determine when or when not to apply a "predominately" close measure to select an area of a cell (e.g. as recited in claims 10 and 11. Those of ordinary skill in the art may well reasonably disagree on the degree of "predominance". Correction or clarification on the record is required.

Claim Objections - 37 CFR 1.75(d)(1)

5. The following is a quotation of 37 CFR 1.75(d)(1):

> The claim or claims must conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.

6. **Claims 18- 19** are objected to under 37 CFR 1.75(d)(1), as failing to conform to the invention as set forth in the remainder of the specification.

Regarding Claims 18 and 19, the term "generally corresponding to" is not defined in applicant's specification. It is unclear as to what area of the cytoplasmic and nuclear

components of a selected cell that applicant intends to claim as his/her own invention. Appropriate correction is required.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims **1-6,8-13,21-23, 33-35** are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (US 5,933,519).

Regarding Claim 1, Lee teaches a method of classifying cells into subpopulations using cell classifying data ("The invention detects areas of interest...locating possible abnormal cells or other cells of interest using image processing and statistical patter recognition techniques..." at column 1, line 35), the method comprising: receiving image data ("The central computer 540 runs a real time operating system, controls the microscope and the processor to acquire and digitize images from the microscope." at column 4, line 56); analyzing said image data to identify object areas in the image data ("...the computer 540 implements a magnification 4x analysis of the slide providing information for the control of further slide processing." at column 4, line 66); analyzing said image data, on the basis of said identified object areas, to determine, for at least

one selected first cell, one or more measurements ("For each 20x region of a 4x image...slide scores are calculated from data gathered during the 4x and 20x scans." at column 5, line 33); deriving a first parameter set for said at least one selected first cell, the first parameter set comprising at least one of said one or more measurements ("The slide suitability score is one of six slide scores that are the results of processing slides on the automated cytology quality control system of the invention. The slide suitability score is derived from measurements of slide characteristics and machine effectiveness." at column 6, line 56); classifying a first set of cells, the process of classifying the first set of cells including classifying said at least one selected first cell into a subpopulation and storing first identifying data indicating the subpopulation into which said at least one selected first cell has been classified (For example, see Figure 2A; "The feature calculation process 7 measures properties such as perimeter or area fro each detected object. After feature calculation 7, the invention compares 8 the feature value for an unknown object to the feature values for know objects 4, allowing the unknown object to be classified 9." at column 5, line 57); deriving cell classifying data for use in classifying a second set cells into subpopulations from said first parameter set and said first identifying data ("Since the single cell analysis is executed before the group analysis on each image, information from the single cell analysis is available to the group analysis for object classification." at column 9, line 1), and classifying a second set of cells into subpopulations on the basis of one or more measurements taken for cells in the second set of cells, by use of said cell classifying

data ("Object classification, object feature results, and error information are passed from the group analysis to the FOV integration analysis." at column 9, line 5).

Regarding Claim 2, Lee teaches wherein said first identifying data is cell cycle phase classifying data ("The following analysis are performed to extract information from the 20x magnification images: single cell analysis, group analysis, thick group analysis, and stripe analysis." at column 5, line 29).

Regarding Claim 3, Lee teaches wherein classifying said second set of cells comprises comparing the measurements for cells in the second set with the cell cycle phase classifying data derived from classification of the first set of cells (For example, Figure 2A, numeral 8; "Some intermediate results must be passed from the FOV processor 568 to computer 540 for later completion of feature calculation and object classification. Figure 2A shows the generic flow diagram for image information extraction." at column 6, line 22).

Regarding Claim 4, Lee teaches wherein classifying said second set of cells comprises calculating a statistical likelihood of each cell in the second set being a member of a subpopulation ("For each 20x region of a 4x images, scores are generated representing the likelihood that the 20x region...contains abnormal cells or cellular groupings." At column 5, line 7).

Regarding Claims 5 and 6, Lee teaches wherein a plurality of measurements are taken, and weighted in statistical importance; wherein applying said cell classifying data to a second set of cells further comprises generating cell cycle phase population data indicative of the relative sizes of said plurality of sub-populations in the selected cells.

("For example, the slide scoring process takes information from the information extraction operation and calculates scores that represent cytological evaluations of a slide." at column 5, line 66; "The computer 540 generates scores after slide scoring analysis such as quality control score (QC score), endocervical score, slide suitability score, and cell count score." at column 5, line 34).

Regarding Claim 8, Lee teaches wherein said object areas are identified using a process arranged to select both nuclear and cytoplasmic areas of a cell ("The single cell analysis detects single, non-overlapping nuclei and cytoplasm within 20x images." at column 8, line 56).

Regarding Claim 9, Lee teaches wherein said object areas include, for a selected cell, a first type of object area and a second type of object area ("Slide scores are calculated from data gathered during the 4x and 20x scans." at column 5, line 32), and wherein said one or more measurements include a first measurement determined using said first type of object area and a second measurement determined using said second type of object area ("The process of detecting objects and calculating measures or features of the objects is shown in FIG. 2A. The object detection process 6 detects objects through image segmentation. These objects represent potential objects of interest." at column 5, line 51).

Regarding Claims 10 and 11, Lee teaches wherein said first type of object area is identified using a process arranged to select a predominantly nuclear area of a cell; wherein said second type of object area is identified using a process arranged to select a predominantly cytoplasmic area of a cell ("The group analysis detects aggregates of

cell nuclei within 20x images. When such objects have been detected, the analysis extracts features for each object and classifies the object as an artifact, possible endocervical, possible metaplastic/parabasal, or possible abnormal group." at column 8, line 64; "Features measured in the cluster area form the most diverse set. They may be calculated from nuclei cytoplasm..." at column 23, line 42).

Regarding Claim 12, Lee teaches wherein said one or more measurements include, for a selected cell, a first measurement determined using an identified object area and a second measurement determined using an identified object area ("The feature calculation process 7 measures properties such as perimeter or area for each detected object." at column 5, line 57).

Regarding Claim 13, Lee teaches wherein said first and second measurements are determined using the same identified object area ("After feature calculation 7, the invention compares 8 the feature value for an unknown object to the feature values for known objects 4, allowing the unknown object to be classified 9. The particular feature representation and classification methods determine the comparison criterion." at column 5, line 58).

Regarding Claim 21, Lee teaches wherein said cell classifying data is used in conjunction with an algorithm (When the 4x scan is completed, the accumulated extracted results are analyzed using the 4x' algorithm 18 and the analysis results 24 are passed back to the computer 540." at column 7, line 37) to classify a selected cell into a selected first one of a plurality of sub-populations of cells ("To provide information for slide scoring, the 4x analysis also derives three histograms--object count, cell count,

and cell to object ratio histogram. These histograms provide measures of object populations on the entire slide." at column 8, line 21).

Regarding Claim 22, Lee teaches wherein the algorithm takes into account a plurality of measurements in a parameter set ("Refer now to FIG. 6 which shows a system interface schematic diagram. A database 70 of results from each slide run is maintained. The interfaces shown ensure that the following calculations and communications occur: The system algorithms 64 process each image and pass results 74 (which includes error conditions if necessary) for that FOV back to the system software 68." at column 10, line 32).

Regarding Claim 23, Lee teaches wherein said one or more measurements include one or more measurements selected from the group consisting of ("A wide range of feature types is necessary for good identification of segmented groups. They can be identified by the kind of information they measure--object shape, size, and texture for example. Or, features can be identified by what part of an image they measure--the object of interest, a small area around the object, the whole image, or combinations of these features." at column 23, line 18): I, a parameter relating to an average signal intensity within an identified object area ("Feature 7 is the average intensity--or pixel value (0 to 255)--of the non-nuclear cluster area." at column 23, line 49); F, a parameter relating to a fraction of pixels that deviate more than a given amount from an average signal intensity within an identified object area ("Feature 111 is the average difference between pixel intensity values two pixels inside good nuclei, and pixel intensity two pixels outside good nuclei." at column 23, line 58); H, a parameter relating to the

number of pixels with a signal intensity below a given threshold within an identified object area ("Feature 149 is the single cell process's low threshold value. This value is calculated during single cell segmentation. It is the result of an adaptive threshold calculation for a certain range of pixel intensities in an image. It gives a measure for how much dark matter there is in an image." at column 28, line 49); A, a parameter relating to a ratio between major and minor axes of an elliptical outline corresponding to an identified object area ("Feature 77 is the magnitude of the 2x1 dark edge in the ring around the cluster. This is the same as Feature 21 except that it's calculated in the ring around the cluster rather than in the cluster." at column 26, line 35); R, a parameter relating to a maximum width of an identified object area ("Feature 21 is the magnitude of the 2.times.1 dark edge. This feature is the same as Feature 14 except that dark pixels are searched for rather than bright regions 3 pixels wide. This measure is of the total amount of dark area covered by single pixels bounded in two directions by bright area." at column 25, line 28); L, a parameter relating to an average width of an identified object area ("Feature 25 is the magnitude of the 9.times.1 dark edge. This feature is the same as Feature 21 except that regions of 7 pixels in width or height are searched for that have bright neighbors." at column 25, line 33); C, a parameter relating to signal texture within an identified object area ("Feature 13 is calculated as the minimum of these two values divided by the sum of the two. It provides a measure of whether there are significantly more relatively bright pixels in one direction versus the other. This feature shows whether there is some directionally dominant texture in the cluster." at column 24, line 54); M, a parameter relating to margination in an identified object area ("Feature

125 is the average perimeter of all nuclei. The perimeter of each nucleus is the average of the perimeter of the nuclear mask and the perimeter of the same mask expanded by one pixel." at column 24, line 16).

Regarding Claim 33, Lee teaches an apparatus arranged to perform the method of claim 1 ("Now refer to Figures 1A, 1B, and 1C which show a schematic diagram of one embodiment of the apparatus of the invention." at column 4, line 10; The details concerning the structure and elements of this apparatus are detailed at column 4, lines 12-55, also see Figure 6). "While features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function." In re Schreiber, 128 F .3d 1473, 1477-78, 44 USPQ2d 1429, 1431-32 (Fed. Cir.1997) Manual of Patent Examining and Procedures 2114.

Regarding Claims 34 and 35, Lee teaches computer software arranged to perform the method of claim 1 and a data carrier storing the computer software of claim 34. ("It is to be understood that the various processes described herein may be implemented in software suitable for running on a digital processor. The software may be embedded, for example, in the central processor 540." at column 4, line 1; also see Figure 6).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention

was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims **7, 14-20** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US 5,933,519) in combination with Dunlay et al. (US 7,117,098 B1).

Lee teaches the elements of the method of claim 1 in the 102 (b) rejections above.

Lee does not teach performing the method with image data from a plurality of wells containing cells, the plurality of wells containing different test compound.

Regarding Claim 7, Dunlay teaches further comprising performing the method with image data from a plurality of wells containing cells, the plurality of wells containing different test compounds ("In a further preferred embodiment, the cell screening system further comprises a reader that measures a signal from many or all the wells in parallel. In another preferred embodiment, the cell screening system further comprises a mechanical-optical means for changing the magnification of the system, to allow changing modes between high throughput and high content screening." at column 6, line 37).

It would have been obvious at the time that the invention was made to add performing the method with image data from a plurality of wells containing cells, the plurality of wells containing different test compounds to the method of claim 1 as taught by Lee because "The signal measured from each well, either fluorescence emission, optical density, or radioactivity, integrates the signal from all the material in the well giving an overall population average of all the molecules in the well." (Dunlay, column 3, line 20)

Lee teaches the elements of the method of claim 1 in the 102 (b) rejections above. Lee does not disclose wherein cells of said first and second sets of cells comprise at least a first luminescent reporter, wherein said step of receiving image data comprises receiving first image data created by detecting radiation emitted by said first luminescent reporter and wherein said step of analyzing said image data to determine one or more measurements comprises analyzing said first image data.

Regarding Claim 14, Dunlay teaches wherein cells of said first and second sets of cells comprise at least a first luminescent reporter ("In one aspect, the present invention relates to a method for analyzing cells comprising providing cells containing fluorescent reporter molecules in an array of locations..." at column 5, line 49), wherein said step of receiving image data comprises receiving first image data created by detecting radiation emitted by said first luminescent reporter ("...a light source having optical means for directing excitation light to cell arrays and a means for directing fluorescent light emitted from the cells to the digital camera..." at column 6, line 21), and wherein said step of analyzing said image data to determine one or more measurements comprises analyzing said first image data ("In another preferred embodiment, the information obtained from high throughput measurements on the same plate are used to selectively perform high content screening..." at column 6, line 8; For examples of these measurement see Figures 20 and 21).

It would have been obvious at the time that the invention was made to add the elements of claim 14 as taught by Dunlay to the method as taught by rejected claim 1, disclosed by Lee because "Fluorescently labeled antibodies are particularly useful reporter

molecules due to their high degree of specificity for attaching to a single molecular target in a mixture of molecules as complex as a cell or tissue." (Dunlay at column 13, line 63.

Lee teaches the elements of the method of claim 1 in the 102 (b) rejections above.

Lee does not disclose [wherein] said step of analyzing said image data to identify object areas comprises analyzing said first image data.

Regarding Claim 15, Dunlay teaches wherein said step of analyzing said image data to identify object areas comprises analyzing said first image data ("In one aspect, the present invention relates to a method for analyzing cells comprising providing cells containing fluorescent reporter molecules in an array of locations..." at column 5, line 49).

It would have been obvious at the time that the invention was made to add the elements of claims 14 and 15 as taught by Dunlay to the method as taught by rejected claim 1, disclosed by Lee because the analysis of the image data allows the user "to rapidly determine the distribution, environment, or activity of fluorescently labeled reporter molecules in cells for the purpose of screening large numbers of compounds..." (Abstract, Dunlay).

Lee also does not disclose the elements of claims 16 and 17. However, **regarding Claim 16**, Dunlay teaches wherein at least one cell in said first and second sets of cells further comprises a second luminescent reporter indicative of the location of a sub-cellular component in a cell ("...analyzing cells comprising providing cells containing fluorescent reporter molecules in an array of locations..." at column 5, line 51).

Regarding Claim 17, Dunlay teaches, wherein said step of receiving image data comprises: a) receiving first image data created by detecting radiation emitted by said first luminescent reporter ("...providing cells containing fluorescent reporter molecules in an array of locations, treating the cells in the array of locations with one or more reagents, imaging numerous cells in each location with fluorescence optics..." at column 5, line 51); and b) receiving second image data created by detecting radiation emitted by said second luminescent reporter ("...imaging numerous cells in each location with fluorescence optics..."at column 5, line 55), wherein said step of analyzing said image data to identify object areas comprises analyzing said second image data, and wherein said step of analyzing said image data to determine one or more measurements comprises analyzing said first image data ("...rapidly determines the distribution, environment, or activity of fluorescently labeled reporter molecules in cells... the method includes computerized means for acquiring, processing, displaying and storing the data received." at column 6, line 5).

It would have been obvious at the time that the invention was made to add the elements of claims 14, 16, and 17 as taught by Dunlay to the method as taught by rejected claim 1, disclosed by Lee because "Fluorescently labeled antibodies are particularly useful reporter molecules due to their high degree of specificity for attaching to a single molecular target in a mixture of molecules as complex as a cell or tissue." (Dunlay at column 13, line 63.

Lee does not disclose the elements of claims 18, 19, and 20. However, **regarding Claim 18**, Dunlay teaches wherein said one or more measurements include a

measurement of cytoplasmic luminescence signal intensity, taken in an area generally corresponding to a cytoplasmic component of a selected cell (For example, see Figure 20; "Most muscular tissue cells contain a sarcoplasmic reticulum, a specialized organelle whose function is to regulate the concentration of calcium ions within the cell cytoplasm. Many nervous tissue cells contain secretory granules and vesicles in which are trapped neurohormones or neurotransmitters. Therefore, fluorescent molecules can be designed to label not only specific components within specific cells, but also specific cells within a population of mixed cell types." at column 14, line 22).

Regarding Claim 19, Dunlay teaches wherein said one or more measurements include a measurement of a nuclear luminescence signal intensity, taken in an area generally corresponding to a nuclear component of a selected cell (For example, see Figure 20, "A specific algorithm measures the amount of probe in the nuclear region (feature 4) versus the local cytoplasmic region (feature 7) of each cell. Quantification of the difference between these two sub-cellular compartments provides a measure of cytoplasm-nuclear translocation (feature 9)."at column 17, line 1).

Regarding Claim 20, Dunlay teaches wherein said step of analyzing said image data to identify object areas comprises analyzing said first image data ("...the information obtained from high throughput measurements on the same plate are used to selectively perform high content screening on only a subset of the cell locations on the plate." at column 6, line 9).

It would have been obvious at the time that the invention was made to add the elements of claims 14, 18, 19, and 20 as taught by Dunlay to the method as taught by rejected

claim 1, disclosed by Lee because "The types of biochemical and molecular information now accessible through fluorescence-based reagents applied to cells include ion concentrations, membrane potential, specific translocations, enzyme activities, gene expression, as well as the presence, amounts and patterns of metabolites, proteins, lipids, carbohydrates, and nucleic acid sequences and nucleic cell identification." at column 3, line 64 (Dunlay).

11. Claims **24-28** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US 5,933,519) in combination with Dunlay et al. (US 7,117,098 B1) and Kuan et al. (US 5,757,954).

Lee teaches the elements of the method of rejected claim 1 as taught in the 102 (b) rejections above. Lee also teaches the claimed elements of claim 24. Lee in combination with Dunlay teaches the elements of rejected claims 7 and 14-20. Lee in combination with Dunlay does not teach the claimed elements of claims 25-28. Although, Lee in combination with Dunlay teach the elements of the claimed elements above, Lee in combination Dunlay does not teach the method of claim 25, further comprising the modeling of a parameter set as a feature vector in an n-dimensional feature space, where n is equal to the number of parameters.

Regarding Claim 24, Lee teaches wherein a second parameter set is derived from said one or more measurements taken for the second set of cells ("Object classification is made by sets of statistical decisions through several levels of classification. Each classifier compares a set of features, unique to that classifier, measured from an object

to decision boundaries which were determined during classifier training." at column 28, line 64).

Kuan in the same field of cell classification teaches:

Regarding Claim 25, Kuan teaches further comprising the modeling of a parameter set as a feature vector in an n-dimensional feature space, where n is equal to the number of parameters ("Since the Parzen Estimator actually computes likelihood values based on where X is located in feature space, the computation result can be approximated by pre-partitioning the whole feature space into many small regions such that all feature vectors that fall within the same region have very similar likelihood values." at column 11, line 51).

It would have been obvious at the time that the invention was made to add further comprising the modeling of a parameter set as a feature vector in an n-dimensional feature space, where n is equal to the number of parameters as taught in rejected claim 25 as taught by Kuan to the combination of the method of Lee and Dunlay as disclosed above because the modeling of the feature vectors would assign "ranking trees" which "based on the estimated probability that feature vector forms the object of interest" or the region of interest at column 11, line 19 (Kuan).

Lee in combination with Dunlay does not disclose [wherein] a feature vector representing said second parameter set and a feature vector representing said first parameter set occupy the same feature space.

Regarding Claim 26, Kuan teaches wherein a feature vector representing said second parameter set and a feature vector representing said first parameter set occupy the same feature space ("FIG. 9 shows an example of two types (x and o) of data samples distributed somewhat as clusters over a 3-D feature space. Depending on the location or distance to each cluster, a feature vector has one of three different probabilities of being class x: r1, r 2, or r3." at column 12, line 1).

It would have been obvious at the time that the invention was made to add a feature vector representing said second parameter set and a feature vector representing said first parameter set occupy the same feature space as taught by Kuan to the method of rejected claim 1 as taught by Lee in combination with Dunlay because the feature vectors of the second set will serve as reference values for the computer software implemented throughout this invention.

Lee in combination with Dunlay does not disclose [wherein] a distance is calculated between the feature vectors.

Regarding Claim 27, Kuan teaches wherein a distance is calculated between the feature vectors ("Features 13 and 14 measure distances between neighboring objects." at column 8, line 54).

It would have been obvious at the time that the invention was made to add [wherein] an application of a measurement of a distance which is calculated between the feature vectors as taught by Kuan to the method of rejected claim 1 as taught by Lee in combination with Dunlay because it would create a calculation of distance for said feature vectors in the computer software claimed in the invention.

Lee in combination with Dunlay also does not disclose [wherein] the distance between the feature vectors is indicative of the classification of the feature vector representing the second parameter set.

Regarding Claim 28, Kuan teaches wherein the distance between the feature vectors is indicative of the classification of the feature vector representing the second parameter set ("A sparse object area ratio feature, sparse object_ area_ ratio calculates the ratio of the total number of segmented sparse object pixels in a 20x zone to the area of that 20x zone." at column 8, line 51).

It would have been obvious at the time that the invention was made to add [wherein] the distance between the feature vectors is indicative of the classification of the feature vector representing the second parameter set to the method of rejected claim 1 as taught by Lee in combination with Dunlay because these calculations of the distances between the feature vectors as disclosed by Kuan would provide the user with the probability of predicating "two probabilistic ranking scores, which are measures of how likely it is for an image to contain cellular information that should be analyzed by the 20x image processing algorithms", for example at column 10, line 63 (Kuan).

Lee in combination with Dunlay also does not disclose [wherein] a cell represented by a feature vector representing the second parameter set is classified according to a calculation of probability.

Regarding Claim 29, Kuan teaches wherein a cell represented by a feature vector representing the second parameter set is classified according to a calculation of probability ("FIG. 9 shows an example of two types (x and o) of data samples distributed

somewhat as clusters over a 3-D feature space. Depending on the location or distance to each cluster, a feature vector has one of three different probabilities of being class x: r1, r 2, or r3. If probability r defined as the ratio of the number of x to the total number of x and o in each cluster or region, then r2 >r3 >r1." at column 12, line 1).

It would have been obvious at the time that the invention was made to add [wherein] a cell represented by a feature vector representing the second parameter set is classified according to a calculation of probability to the method of rejected claim 1 as taught by Lee in combination with Dunlay because "The process of classification is hierarchical. The rationale of the hierarchies is to reject and assign minimum ranks to field of views or objects of interest that are very unlikely to contain objects of interest at the early stages. Finally, the remaining objects are passed to the last stage probabilistic ranker to assess the appropriate rank for them. Note that the minimum rank assigned at the later stage is always equal to or higher than those at the earlier stage." at column 11, line 8 (Kuan).

Lee in combination with Dunlay also does not disclose [wherein] the calculation of probability comprises calculating the likelihood that the cell represented by said feature vector representing the second parameter set is in the same subpopulation as a cell represented by a feature vector representing the first parameter set, the calculation being based on the dimensions of the feature vectors.

Regarding Claim 30, Kuan teaches wherein the calculation of probability comprises calculating the likelihood that the cell represented by said feature vector representing the second parameter set is in the same subpopulation as a cell represented by a

feature vector representing the first parameter set, the calculation being based on the dimensions of the feature vectors ("Probability Density Estimation--With this data set, a non-parametric Parzen probability density estimation method 96 is used to compute the probability distributions over the M feature spaces. Parzen Estimation is one method of estimating the data probability distribution, given that the data set is adequately representative and the feature dimensionality is not too high...The probability density function value at every feature point is estimated by using all the other feature samples in the training set T. Once the nonparametric Parzen Estimator, using all the training samples of T, has estimated the probability, we will then be able to use the trained Estimator to assign likelihood to unknown feature vector X." at column 11, line 37).
It would have been obvious at the time that the invention was made to add [wherein] the calculation of probability comprises calculating the likelihood that the cell represented by said feature vector representing the second parameter set is in the same subpopulation as a cell represented by a feature vector representing the first parameter set, the calculation being based on the dimensions of the feature vectors to the method of rejected claim 1 as taught by Lee in combination with Dunlay because "those objects that have a higher possibility or likelihood are passed down further into the hierarchy, where more features and finer classifiers are used to eliminate unlikely objects." At column 11, line 12 (Kuan). This allows the user to have and utilize a more efficient software and this calculation provides a closer determination of the classification of the parameter sets based on the dimensions of the feature vectors.

12. Claims **31, 32** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US 5,933,519) in combination with Dunlay et al. (US 7,117,098 B1) and further in view of Riley et al. (US 6,453,060 B1).

Lee teaches the elements of the method of rejected claim 1 as taught in the 102 (b) rejections above. Lee in combination with Dunlay teaches the method of claim 25. Lee in combination with Dunlay does not disclose wherein a neural network is applied to classify the cell represented by a feature vector representing the second parameter set with respect to the feature vector representing the first parameter set nor [wherein] said cells comprise a nucleic acid reporter construct, preferably a DNA construct, comprising a nucleic acid sequence encoding a detectable live-cell reporter molecule operably linked to and under the control of: i) at least one cell cycle phase-specific expression control element, and ii) a destruction control element.

Regarding Claim 31, Riley teaches wherein a neural network is applied to classify the cell represented (Object classification may be accomplished using methods that include, but are not limited to, rule-based decision trees and, alternatively, artificial neural networks." at column 5, line 14) by a feature vector representing the second parameter set with respect to the feature vector representing the first parameter set ("However, cross-connections shown by connection 41 between branches 38A and 38B, for example, may serve to allow the segmentation masks for one image to select pixels for feature calculation in another branch. Features from a first branch may also modify the outcome of processing in a second branch." at column 5, line 21).

It would have been obvious at the time that the invention was made to add a neural network [where it is] applied to classify the cell represented by a feature vector representing the second parameter set with respect to the feature vector representing the first parameter set to the method of rejected claim 1 as taught by Lee in combination with Dunlay because "The invention relates to the use of molecular markers in an automated microscope utilizing computer image analysis for biological specimens." at column 1, line 8 (Riley).

Lee in combination with Dunlay also does not teach [wherein] said cells comprise a nucleic acid reporter construct, preferably a DNA construct, comprising a nucleic acid sequence encoding a detectable live-cell reporter molecule operably linked to and under the control of: i) at least one cell cycle phase-specific expression control element, and ii) a destruction control element.

Regarding Claim 32, Riley teaches wherein said cells comprise a nucleic acid reporter construct ("The molecular marker stain 14 may comprise an antibody and associated dye or a nucleic acid and associated dye or any other molecular light absorbing dye." at column 3, line 41), preferably a DNA construct ("...may be a cervical cancer smear, blood sample, sputum specimen, urine, bone marrow, spinal fluid or any other cellular biological specimen." at column 3, line 36), comprising a nucleic acid sequence encoding a detectable live-cell reporter molecule operably linked to and under the control of: i) at least one cell cycle phase-specific expression control element, and ii) a destruction control element ("A variety of alternative configurations of the apparatus are equally applicable to the invention. The wavelength selection can be accomplished in

the light path between the objective and the camera, for example. Furthermore, separate cameras, each having its own optical filter at a particular wavelength can be utilized to allow simultaneous collection of multiple images." at column 4, line 37).

It would have been obvious at the time that the invention was made to add [wherein] said cells comprise a nucleic acid reporter construct, preferably a DNA construct, comprising a nucleic acid sequence encoding a detectable live-cell reporter molecule operably linked to and under the control of: i) at least one cell cycle phase-specific expression control element, and ii) a destruction control element to the method of rejected claim 1 as taught by Lee in combination with Dunlay because "When such biochemical markers are used in conventional microscopy, a trained specialist views the image from the microscope and searches for structures of the color produced by the chromogen of interest. A judgment is then made of the clinical significance of the appearance, if any, of the marker. This judgment may be based on the identification of cell type and degree of morphological abnormality of the cells stained by the marker as well as the concentration of the marker stain." Therefore, it is one motivation of the invention to provide an automated screening system that uses this information to automatically analyze a biological specimen. "It is a further object of this invention to separate molecular marker information from morphological features." at column 1, line 59 (Riley).

Double Patenting

13. Claim 23 of this application (10/817,213) conflict with claim 24 of Application No. (10/550,362). 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822..

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 16 of copending Application No. 10/550,362. The conflicting claims are not identical because the copending application No. 10/550,362 requires the additional step, referring to Claim 1, "...including a measurement of a parameter relating to at least a cytoplasmic component of the cell..." at page 3, line 15; "...which include at least one luminescent reporter capable of emitting radiation, the at least one luminescent reporter including first luminescent reporter which is capable of being indicative of at least one cell cycle phase..." at page 3, line 4 (No. 10/550, 362) not required by claim 1 of (No. 10/817,213). However, the conflicting claims are not patentably distinct from each other because: Claim 16 of application (No. 10/550,362) and Claims 1 of application (No. 10/817,213) recite common subject matter.

Whereby claim 1(No. 10/817,213), which recites the open ended transitional phrase "comprising", does not preclude the additional element "...including a measurement of a parameter relating to at least a cytoplasmic component of the cell..."; "...which include at least one luminescent reporter capable of emitting radiation, the at least one luminescent reporter including first luminescent reporter which is capable of being indicative of at least one cell cycle phase..." recited by claim 16.

Whereby the elements of claim 1 (No. 10/817,213) are fully anticipated by copending application claim 16 (No. 10/550,362), and anticipation is "the ultimate or epitome of obviousness" (In re Kalm, 154 USPQ 10 (CCPA 1967), also In re Dailey, 178 USPQ 293 (CCPA 1973) and In re Pearson, 181 USPQ 641 (CCPA 1974)).

16. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mia M. Thomas whose telephone number is 571-270-1583. The examiner can normally be reached on Monday-Friday 7:30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Werner can be reached on 571-272-7401. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MMT

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